

ORIGINAL ARTICLE

Neoadjuvant chemoradiotherapy followed by liver transplantation for unresectable cholangiocarcinoma: a single-centre national experience

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Abstract

Background: Unresectable cholangiocarcinoma (CCA) has a dismal prognosis. Initial studies of orthotopic liver transplantation (OLT) alone for CCA yielded disappointing outcomes. The Mayo Clinic demonstrated long-term survival using neoadjuvant chemoradiotherapy followed by OLT in selected patients with unresectable CCA. This study reports the Irish National Liver Transplant Programme experience of neoadjuvant therapy and OLT for unresectable CCA.

Materials and Methods: Twenty-seven patients with CCA were selected for neoadjuvant chemoradiotherapy in a single centre from October 2004 to September 2011. Patients were given brachytherapy, external beam radiotherapy and 5-fluorouracil (5-Fu), followed by liver transplantation if progression free (20 patients).

Results: Twenty progression-free patients after neoadjuvant therapy underwent OLT. Hospital mortality was 20%. Of the 16 patients who left hospital, survival rates were 94% and 61% at 1 and 4 years. Seven patients developed recurrent disease and died at intervals of 10–58 months after OLT, whereas 9 are disease free with a median follow-up of 37 months (18–76). Predictors of disease recurrence were a tumour in explant specimen and high CA 19.9 levels.

Discussion: In selected patients with unresectable CCA, long-term survival can be achieved using neoadjuvant chemoradiotherapy and OLT although short-term mortality is high. Prospective international registries may aid patient selection and refinement of neoadjuvant regimens.

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Introduction

Cholangiocarcinoma occurs in two principal settings. First, it may arise 'de novo' in patients with no underlying biliary tract pathology. In this situation, it most commonly occurs in the hilar region (50–60% of cases), at the confluence of the right and left hepatic ducts (i.e. Klatskin tumour).¹ Second, it may arise in the setting of pre-existing primary sclerosing cholangitis (PSC).² In either case, the surgical options are limited and the surgical outcomes are disappointing. In the case of hilar

cholangiocarcinoma (hilar CCA) barely 25% of patients are suitable for surgical resection, which usually involves an extended hepatectomy.³ Furthermore, the 5-year survival is just 25–30% in most series.^{4–6} In the case of PSC cholangiocarcinoma (PSC CCA) the surgical options are even more limited because of the underlying liver disease and because of the frequently multifocal nature of the tumour.²

Almost 20 years ago, the Mayo Clinic proposed a novel strategy of neoadjuvant chemo radiotherapy followed by liver transplantation for unresectable cholangiocarcinoma.⁷ This was based on a concept originally proposed at the University of Nebraska⁸ and has become widely known as the 'Mayo Protocol'. The Mayo Protocol involves external beam radiotherapy (40–45 Gy delivered

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over 3 weeks), followed by transcatheter brachytherapy at a dose of 20–30 Gy as a single dose. Infusional 5-fluorouracil (5-FU) is given during the radiotherapy. The patients are maintained on oral capecitabine while awaiting orthotopic liver transplantation (OLT). The Mayo Clinic group have published regular updates on the results of this treatment strategy^{9–11} and have most recently published an update on 136 patients with 1-, 3- and 5-year survivals of 92%, 81% and 74%, respectively.¹¹ In spite of these truly outstanding results, this treatment strategy has not yet been widely adopted around the world.

In 2004, based on early reports from the Mayo Clinic, our unit undertook a pilot study of a neoadjuvant therapy/liver transplantation regime for carefully selected patients with unresectable cholangiocarcinoma. Our programme is a single centre national programme, serving a population of 4.2 million, which has performed more than 750 liver transplants and currently performs 60–65 liver transplant procedures each year.

Patients and methods

Patient group

Twenty-seven patients at a single National Liver Transplant Centre were considered for neoadjuvant chemo radiotherapy followed by OLT between October 2004 and September 2011. There were 25 males and 2 females, with an age range of 24–67 years. All patients had a diagnosis of either unresectable 'de novo' hilar cholangiocarcinoma (hilar CCA) or cholangiocarcinoma arising in the setting of underlying primary sclerosing cholangitis (PSC CCA).

The patients with hilar CCA were deemed unresectable based on radiological appearances and after assessment by at least two Hepato-Pancreato-Biliary surgeons and formal presentation/discussion at our institutional Multidisciplinary Team (MDT) meeting. The patients with PSC CCA were considered based on the emergence of a dominant or suspicious stricture in patients with established PSC.

Assessment

The preliminary work up of the patients was designed to: (i) determine the size of the primary tumour mass; (ii) establish a definite tissue diagnosis; and (iii) exclude spread beyond the immediate locoregional area. Patients were excluded if they had a tumour mass greater than 3 cm on cross-sectional imaging. A definitive tissue diagnosis was attempted by either histological (endoluminal biopsy) or cytological (biliary brushing) examination after percutaneous drainage. All tissue specimens were examined by an experienced biliary pathologist and reviewed at the MDT meeting. A computed tomography (CT) scan of thorax, abdomen and pelvis was used to exclude systemic spread of the tumour and to determine the degree of any vascular involvement. Vascular encasement of the hepatic artery was not a contraindication to the treatment protocol. Patients were excluded if they had an open or transperitoneal biopsy of the tumour

mass or if they had previous attempted surgical treatment or chemotherapy.

Neoadjuvant treatment

The patients selected for the treatment protocol then proceeded to the neoadjuvant treatment regime. Patients received a single dose of brachytherapy, delivered by a percutaneous transhepatic catheter. The typical dose was 7.5 Gy prescribed at a distance of 1 cm from the central plane. The maximum active length was 12 cm. The isotope was high-dose rate Iridium 192 mounted on a retractable wire (Gammamed system) and the treatment times varied from 10–20 min. The patients also received external beam radiotherapy, 45–55Gy (usually 50Gy), delivered at a dose of 2 Gy per day, for 5 days per week over 5 weeks. Treatment planning CT scans were used and the gross target volume consisted of any radiologically visible tumour. The clinical target volume included the gross target volume plus the hilar lymph nodes and, in some instances, the adjacent para-aortic nodes. The planning target volume included the clinical target volume plus 1 cm. Three-dimensional conformal techniques were used to design and deliver the radiotherapy using minimum energy of 6 MV. Standard dose volume constraints were used for the organs at risk. The patients also had a 5-FU infusion of 1000 mg/m²/day for 4 days during week 1 and again during week 5 of the external beam radiotherapy. Finally, they had maintenance capecitabine at a dose of 2000 mg/m²/day (in two divided doses) for 2 weeks out of every 3 while on the waiting list for OLT.

Final assessment

On completion of neoadjuvant treatment, the patients underwent either a formal laparotomy (preferably) or a laparoscopy. Excision biopsy of a lymph node in the hepatic pedicle was performed and any other suspicious or enlarged nodes were also excised for biopsy. A full examination of the peritoneal surface was also performed and biopsy of any suspicious lesions was performed. The liver was carefully examined by palpation and by per-operative ultrasonography. Finally, peritoneal washings were obtained for cytological examination. No attempt was made to biopsy the tumour mass.

The patients were then formally presented at our Liver Unit MDT and were placed on the waiting list for OLT if they had no exclusion criteria and were otherwise fit for transplantation. They were maintained on oral capecitabine as described above while on the waiting list. CT scans of the thorax, abdomen and pelvis were repeated if patients were more than 4 months on the waiting list.

Surgical treatment

At liver transplantation, a preliminary careful inspection of the peritoneum and liver was performed and a frozen section biopsy was undertaken for any suspicious lesions. The OLT was a standard caval replacement procedure. The portal vein was taken low, near the first part of the duodenum. Arterial reconstruction was performed using an iliac artery conduit from the infra renal anterior aorta, because of potential radiation damage to the native

hepatic artery. Biliary drainage was by Roux-en-Y hepaticojejunostomy. Post-operatively, patients were maintained on standard dual therapy of tacrolimus and steroids. Tumour surveillance was by CT thorax, abdomen and pelvis (CT-TAP) and carbohydrate antigen 19-9 (CA19-9), performed every 6 months for 2 years and annually thereafter.

Statistical analysis

Survival figures were analysed for 1-year actual survival and 2-, 3- and 4-year actuarial survival (Kaplan–Meier). The numbers were too small to conduct 5-year survival analysis. Analysis of factors influencing outcome was performed using the chi-square test and Fisher’s exact test. Statistical significance was considered at $P < 0.05$ where numbers were sufficient to allow meaningful statistical analysis.

Results

Of the 27 patients who were initially considered for the treatment regime, 7 were subsequently excluded because of disease extent or disease progression whilst undergoing neoadjuvant treatment or whilst awaiting OLT. These 7 patients are not considered further in this report. A total of 20 patients therefore proceeded to OLT and are the subjects of this study. There were 19 males and 1 female, age range 24–67 years.

Six patients (30%) required simultaneous pancreaticoduodenectomy (Whipple’s operation) either because of radiation effect (3 patients) or because of disease location/extent in PSC-CCA patients (3 patients). The need to perform a Whipple’s procedure was determined at the time of surgery. Three patients (15%) required re-transplantation at 2 days, 29 days and 41 days after initial OLT. The indications for re-transplantation were hepatic artery thrombosis (2 patients), and portal vein thrombosis (1 patient). The median duration of surgery was 5 h (range 3.7–8.4) and the median hospitalisation was 18 days (12–109).

There were 4 hospital deaths at 3 days, 35 days 55 days and 109 days after OLT (20% hospital mortality). The causes of hospital death are summarised in Table 1. Two of the 4 deaths (50% of the

hospital mortality) were patients who had simultaneous OLT plus Whipple’s operation. The other 2 deaths were patients who required re-transplantation. Therefore, all of the hospital mortality occurred in patients who either required simultaneous Whipple’s operation or who required re-transplantation.

Sixteen patients (80%) left hospital alive. Among this group, 7 patients subsequently developed recurrent disease and died at 10, 12, 15, 17, 41, 52 and 58 months after OLT (Fig. 1). The remaining 9 patients (56%) are currently alive and disease free at a median 37 months after OLT (Fig. 1). The survival figures for the entire group of 20 patients are 75% at 1 year (actual), and 60%, 60%, and 51% at 2, 3 and 4 years (actuarial). The survival figures for the 16 patients who left hospital (i.e. censored for hospital deaths) were 94% at 1 year (actual) and 73%, 73% and 61% at 2, 3 and 4 years (actuarial) (Fig. 2).

Six patients in the group were over 60 years of age at the time of OLT and a further 5 patients were aged 50–59 years. The 4 peri-operative deaths all occurred among the 11 patients who were over 50 years of age. However, among the 16 patients who left hospital alive, the survival figures were not influenced by age over 50 years or under 50 years.

There were 4 patients with hilar CCA and 16 patients with PSC CCA. All 4 patients with hilar CCA developed recurrent disease and died at 10, 17, 41 and 58 months after OLT. Among the PSC CCA patients (16 patients) there were the 4 hospital deaths and 3

Table 1 Causes of hospital mortality

Operation	Post-operative course/cause of death	Survival time (days)
OLT	➤ Primary graft non-function	3
	➤ Retransplant	
	➤ Arrest	
OLT and Whipples	➤ DIC/multiorgan failure	35
OLT and Whipples	➤ Hepatic artery thrombosis	55
OLT	➤ Hepatic artery thrombosis	109
	➤ Retransplant	
	➤ Pancreatic leak	
	➤ Hepatic artery bleed	
	➤ Multiple laparotomies	
	➤ Sepsis	
	➤ Haemorrhage	

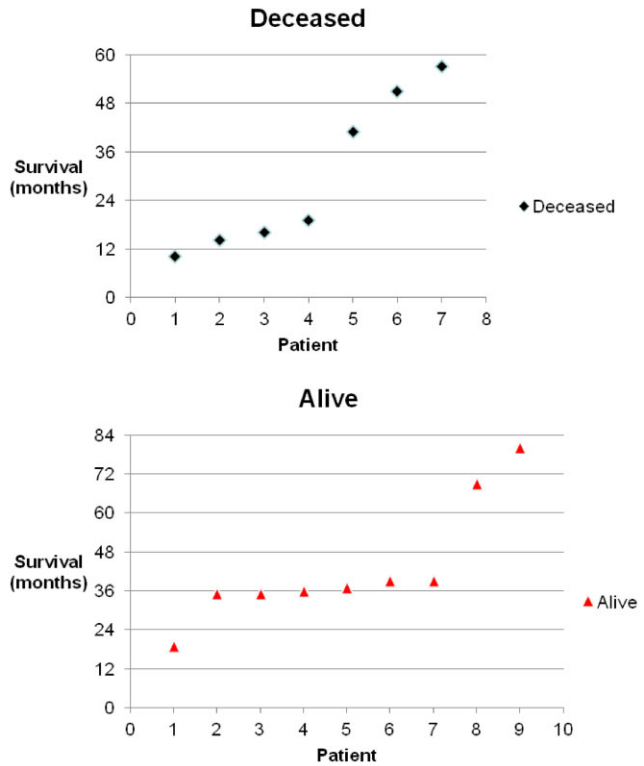


Figure 1 Mortality and survival data

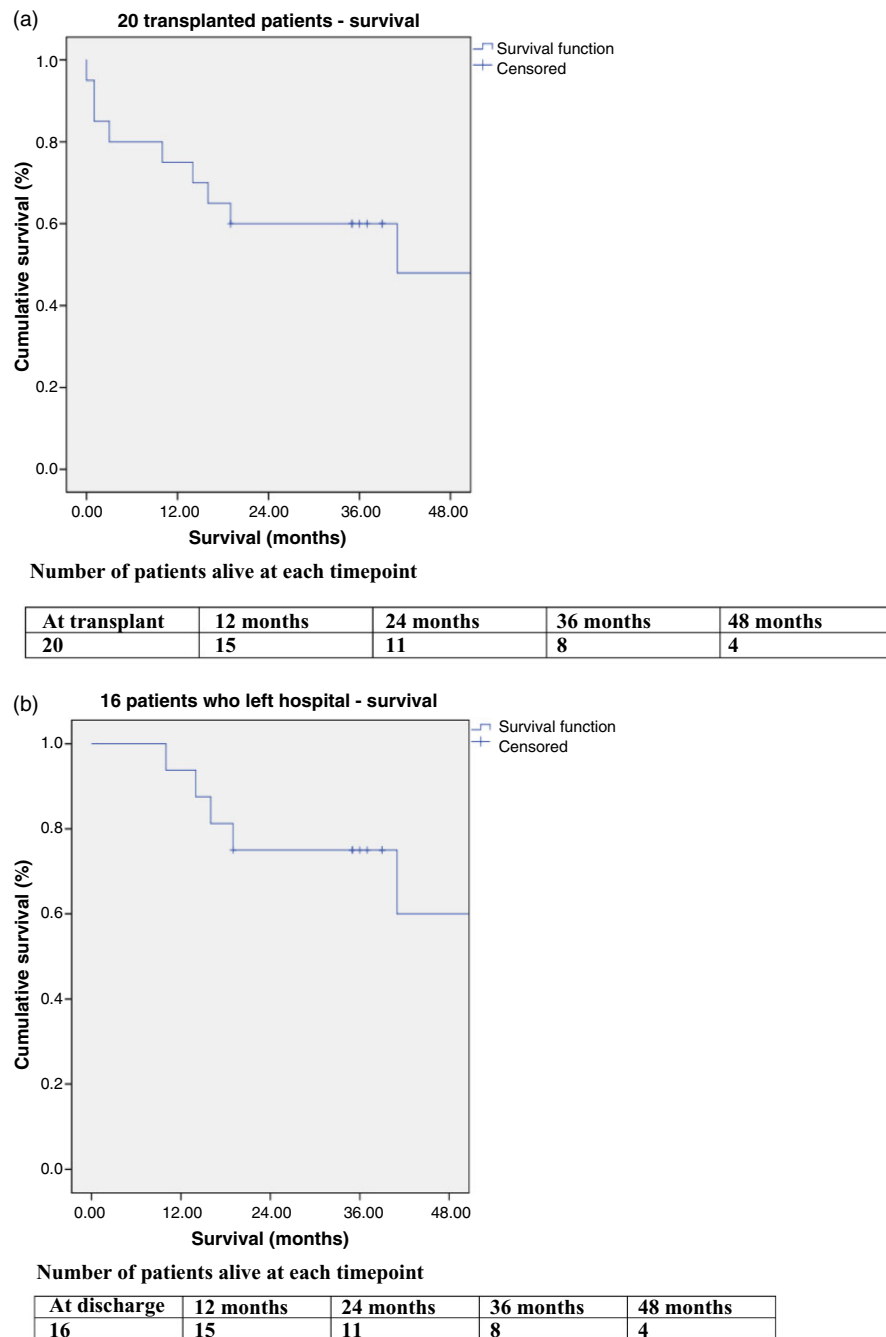


Figure 2 Kaplan–Meier survival curves (a) for all 20 patients; and (b) for 16 patients who left hospital alive. Number of patients alive at each time point

deaths from recurrent disease at 12, 15 and 52 months post-OLT. There are 9 PSC CCA patients alive and disease free at 18–76 months (median 37 months) after OLT.

All except two patients had a definite tissue diagnosis of CCA prior to undergoing the neoadjuvant treatment protocol (either histology or cytology). The two patients without a definite diagnosis had highly suspicious imaging combined with high CA19-9

(>100). Both of these patients had a tumour in the explant specimen and subsequently developed recurrent disease and died at 12 and 15 months. It can therefore be concluded that all patients in this series had a definite diagnosis of malignancy, either by histology/cytology or by subsequent disease evolution.

Although brachytherapy was considered to be an important part of the ‘intention-to-treat’ strategy, in fact only 11 patients

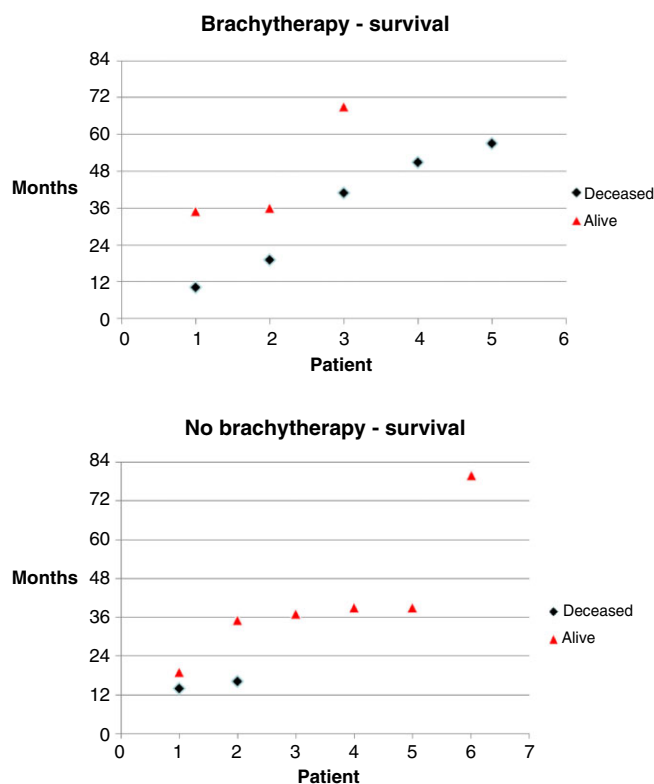


Figure 3 Effect of brachytherapy or no brachytherapy on survival

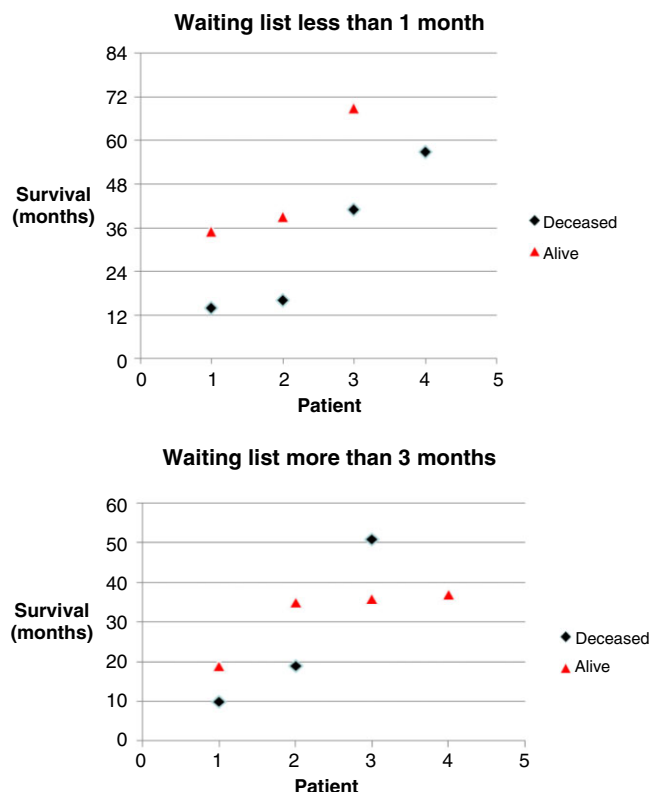


Figure 4 Effect of waiting time for liver transplantation on survival

received brachytherapy. For nine patients, it was not possible, for technical reasons, to place the transhepatic catheter or to position the iridium wire in the appropriate position. Of the 16 patients who left hospital alive, 8 had received brachytherapy (of whom 3 are alive and disease free, 37%) whereas 8 did not receive brachytherapy (of whom 6 are alive and disease free, 75%) (Fig. 3).

Seven patients were less than 1 month on the waiting list for a liver transplant and 7 patients were more than 3 months on the waiting list (longest wait was 217 days, i.e. 7 months). There was no difference in recurrence rates or survival between those with a short waiting time and those with prolonged waiting times (Fig. 4).

Among the 20 patients, there were 9 patients who had a viable tumour in the explant specimen and 2 patients had positive lymph nodes (in spite of negative nodes at staging laparotomy). All except 2 of the 9 patients with a viable tumour had received brachytherapy. Among the 16 patients who left hospital alive, 7 had a viable tumour in the explant specimen. Of these, 6 developed a recurrent tumour and died at 12, 15, 17, 41, 52 and 58 months. Just 1 patient with a viable tumour (and positive lymph nodes) is currently alive and well at 66 months post-OLT.

Pre-operative CA19-9 levels are available on 14 of the 20 patients. Six patients had CA19-9 levels >100 and 8 patients had CA19-9 levels < 100. Patients with high CA19-9 levels were more likely to have a tumour in the explant specimen (5 of 6 patients)

and to develop recurrent disease and die. Patients with low CA19-9 levels were more likely to have no residual tumour in the explant specimen (8 of 8 patients) and to be alive and disease free (7 of 8 patients) (Fig. 5). Patients who developed recurrent disease and died (7 patients) all had a residual viable tumour in their explant specimen and elevated CA19-9 levels. Five of these 7 patients had received brachytherapy and 4 of the 7 patients were waiting less than 1 month for OLT. In contrast, among the 9 patients who are currently alive and well, 8 had no residual tumour in the explant specimen and 7 out of 8 patients (one missing value) had low CA19-9 levels. Only 3 of these 9 patients had received brachytherapy and 5 of the 9 patients were waiting more than 3 months for OLT.

Discussion

Barely 25–30% of patients with hilar CCA are surgically resectable.³ Furthermore, the results of a surgical resection for hilar CCA are characterized by high hospital mortality, high complication rates and poor long-term survival.¹¹ When CCA occurs in the setting of PSC, the surgical options are even more limited and the results are likewise poor.¹² For these reasons, a liver transplantation appears to present an attractive concept for these patients because it allows radical resection with a guaranteed tumour-free resection margin and it also treats the underlying PSC when

CA 19.9 > 100: 6 patients

	Status	Time (Months)	Tumour in explant
1.	Dead	52	Yes
2.	Dead	58	Yes
3.	Dead	15	Yes
4.	Dead	1.2	Yes
5.	Dead	17	Yes
6.	Alive	17	No

CA 19.9 < 100: 8 patients

1.	Alive	76	No
2.	Alive	41	No
3.	Alive	38	No
4.	Alive	35	No
5.	Alive	28	No
6.	Alive	36	No
7.	Alive	26	No
8.	Dead	1.8	No

Figure 5 Relationship of carbohydrate antigen 19-9 (CA19-9) levels to survival status and to presence of a viable tumour in explant specimen

present. In the early years of liver transplantation (1960s and 1970s), cholangiocarcinoma was a relatively frequent indication for liver transplantation. However, the results did not live up to expectation and recurrence rates were unacceptably high.¹³ As a result, cholangiocarcinoma became a contraindication for liver transplantation in most centres.¹⁴ The emergence of neoadjuvant chemoradiotherapy has rekindled interest in the role of liver transplantation for CCA and this approach has been largely pioneered by the Mayo Clinic group.^{15,16} The present study of a small group of patients with unresectable CCA, treated by neoadjuvant chemoradiotherapy followed by liver transplantation in a single national centre, has shown superior results to those of surgical resection. Overall 1-, 3- and 4-year survivals were 75%, 60% and 51%, respectively. However, when the data were censored for hospital deaths, the disease-related 1-, 3- and 4-year survivals were 94%, 73% and 61%, respectively.

The results published on a regular basis by the Mayo Clinic group have shown significantly better outcomes than reported in the present series. From the time of the first report in 2000, there were excellent results.⁷ The second report, in 2004,⁹ showed 92%, 82% and 82% 1-, 3- and 5-year survivals among 38 patients. By 2008, the series had grown to 111 patients with 96%, 83% and 72% 1-, 3- and 5-year survivals.^{10,17} At that time, they reported just 15 recurrences in 111 patients. The latest updates, in 2012, show 92%, 81% and 74% 1-, 3- and 5-year survivals among 136 patients.^{11,18} Furthermore, the latest report includes patients from 11 other institutions in the United States, a cumulative experience of 214 patients. Considering that the Mayo Clinic contributed 131 patients to this series, it is clear that most of the other 11 centres contributed very small numbers of patients.¹⁸ One of the most perplexing features of this treatment strategy for unresectable

cholangiocarcinoma is that it has not been widely adopted around the world, in spite of the excellent reports from the Mayo Clinic group and other US centres.¹⁹

Part of the reason for our poorer results (as compared with the Mayo Clinic) undoubtedly relates to high hospital mortality (20%). This is largely accounted for by the high percentage of our patients (30% versus 9% in latest Mayo report¹⁸) who required Whipple's operation (2 of our 4 hospital deaths had Whipple's operation plus OLT) and the need to perform re-transplantation (2 of our 4 hospital deaths). Most of our simultaneous Whipple's operations were performed early in our series because of a radiation effect around the hepatic pedicle, making safe dissection in this area impossible. Subsequent alterations in the radiotherapy administration protocol have resulted in less radiation effect in this region and a lower requirement for performing Whipple's procedure. On the other hand, it should be noted that our 2 longest survivors (66 and 76 months) were PSC CCA patients who had a simultaneous Whipple's procedure plus OLT.

In our series, the results of neoadjuvant chemo radiotherapy followed by liver transplantation appear to have been worse for patients with hilar CCA than for patients with PSC CCA. The 4 patients with hilar CCA all developed recurrent disease and subsequently died. However, 2 of these patients survived 41 and 58 months. These numbers are certainly too small to make any valid conclusion. On the other hand, among the 12 hospital survivors with PSC CCA, only 3 patients developed recurrent disease and 9 remain disease free at a median of 37 months after treatment.

All of the patients in our series had a definite tissue diagnosis of cholangiocarcinoma. In the vast majority of patients (18 of 20 patients) there was a definite diagnosis prior to commencing neoadjuvant chemo radiotherapy, either by endoluminal biopsy/histology or by biliary brushings/cytology. Two patients did not have a definite tissue diagnosis prior to neoadjuvant therapy but had characteristic radiological appearances together with markedly elevated CA19-9 levels. In fact, both of these patients had a tumour in the explant specimen and developed recurrent disease and died from disseminated cholangiocarcinoma at 12 and 15 months, indicating that they did indeed have definite cholangiocarcinoma from the outset. In the Mayo Clinic series, barely 50% of the patients had a definite tissue diagnosis before treatment. However, approximately one-half of those without a tissue diagnosis had subsequent proof of diagnosis, either on explant histology or by disease progression.¹⁸ Furthermore, the Mayo results are still excellent even when the patients without a tissue diagnosis are excluded from the analysis.

Although brachytherapy was an integral part of our neoadjuvant regime, in fact, 9 patients (45%) did not receive brachytherapy but still continued on the treatment protocol. This was because of technical problems in patients with PSC causing an inability to place a percutaneous transhepatic catheter in the appropriate bile duct or place the iridium pellet in the correct location. These patients just received external beam radiotherapy plus chemotherapy. Contrary to expectation, this did not have a

negative impact on the outcome. In fact, of the 16 hospital survivors, 8 had received brachytherapy (among whom there were 5 recurrences and deaths, 61%) and 8 did not receive brachytherapy (with only 2 recurrences and deaths, 25%). Again, the numbers are too small to allow statistical analysis but there certainly are questions to answer about the role of brachytherapy in these patients. Although the Mayo group give brachytherapy, they also state that brachytherapy is technically difficult and resource intensive and that exact placement of the Iridium beads/pellet can be challenging. In their analysis, they conclude that there is no added benefit in giving brachytherapy compared with external beam radiotherapy alone.¹⁸

Another unexpected finding in our series is that the time on the transplant waiting list did not appear to affect the likelihood of recurrence and death. Patients who were waiting 1 month or less on the transplant waiting list appear to have fared no better than patients who were waiting more than 3 months on the waiting list. In fact, the 2 longest survivors in our series were waiting more than 6 months on the waiting list.

The single most important factor in determining long-term outcome in our series appears to be the presence or absence of a residual tumour in the explant liver specimen. Of the 16 patients who left hospital, 7 had a residual tumour in the explant specimen and 9 had a complete pathological response with no residual tumour in the specimen. Among the 7 patients with a residual tumour, 6 developed recurrent disease and died and just 1 patient is currently alive and disease free (at 66 months). On the other hand, among the 9 patients with no residual tumour, no patient has developed recurrent disease, although one patient died from unrelated causes. Although this prognostic indicator is very important, it is of limited usefulness because the information only becomes available after the treatment (including OLT) has been completed. It would indeed be very useful if there was a predictive indicator for a tumour in the explant specimen. In our series, the CA19-9 was highly predictive of a tumour in the explant specimen. We divided our patients into two groups: those with CA19-9 > 100 and those with CA19-9 < 100. Among 6 patients with high CA19-9, 5 had residual tumour in the explant specimen and all developed recurrent disease and died. Just 1 patient in this group remains alive and disease free (with no tumour in the explant specimen) at 17 months after OLT. Among 8 patients with low CA19-9 levels, no patient had a residual tumour in the explant specimen and 7 of these 8 patients are alive and disease free, the eighth patient having died as a hospital mortality. The Mayo Clinic group also found that the presence of a tumour in the explant specimen and an elevated CA 19-9 level had a negative impact on outcome. Other factors which they identified as having a negative effect included older age, prior cholecystectomy, perineural spread and advanced tumour grade.¹⁵

There exists considerable controversy around whether it is justifiable to use donor livers (a scarce resource) for the treatment of unresectable cholangiocarcinoma. This controversy could be addressed from the perspective of a liver transplant surgeon or

from the perspective of a surgical oncologist. From a liver transplant surgeon's perspective, our results would certainly constitute a 'borderline' indication for OLT. However, the results are at least as good as results for other 'borderline' indications such as patients who are co-infected with Hepatitis C plus HIV.^{20,21} From a surgical oncologist's perspective, there is no controversy; these results are far superior to the results of a surgical resection and these results were achieved in patients with unresectable disease. Indeed, the Mayo Clinic group are now understandably making the case for 'Mayo Protocol' plus OLT for patients with resectable hilar CCA.^{18,22}

In conclusion, we have not been able to reproduce the excellent results achieved by the Mayo Clinic. However, we have shown that a carefully selected group of patients, all with a definite diagnosis of cholangiocarcinoma, can achieve very worthwhile survival results: results which are certainly better than most published results for surgical resection. We believe that this approach is worthy of ongoing evaluation and we encourage a European cooperative evaluation.²³

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Author contributions

Study conception and design: Maguire, Fennelly, Armstrong; Acquisition of data: Duignan, Ravichand, Mohan, Rock; Analysis and interpretation of data: Traynor, Duignan, Mohan, Maguire, Hoti, Geoghegan; Drafting of manuscript: Traynor, Mohan, Duignan; Critical revision of manuscript: All authors.

Conflicts of interest

None declared.

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